


# In-vitro Evaluations of Quality Control Parameters of Paracetamol Tablets Marketed in Gondar City, Northwest Ethiopia

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**Background:** The aim of this research was to evaluate quality control parameters of available brands of paracetamol tablets in Gondar city since standard quality parameters are essential for a better quality of the product. The different brands of paracetamol tablets were obtained from local pharmacies in Gondar town and the University of Gondar (UOG) hospital pharmacies.

**Methods:** Five brands of paracetamol, from each, 102 tablets were collected from private pharmacies, government health centers, and UOG pharmacies. The popular brands in the city, Panadol, Para-denk, Paramol, Paracetamol (EPHARM), and Cadimol, conventional tablets of 500 mg strength were chosen and the tablets were assessed for different quality parameters: weight variation, hardness, friability, disintegration, dissolution, and drug content (assay) using compendial methods. The tablets were evaluated to check if they comply with the specifications of USP (United States Pharmacopeia).

**Results:** From the results, it was observed that all the brands of paracetamol have passed the tests and met the specifications of USP. Results of weight variation, hardness, friability, and disintegration time ranged from 0.46 to 1.11%, 117.0 to 174.70 N, 0.07 to 0.63%, and 01 to 08 minutes for all the tablets, respectively. The dissolution profiles of all the brands are within the acceptable label claim. The assay results showed that the drug content of the paracetamol brands ranged from 95.04% to 106.81%. The dissolution rate was significantly different ( $p < 0.05$ ) as compared to code 1 with all brands tested at 30 minutes. The disintegration time of different brands was also significantly different from the comparator (code 1) except code 2.

**Conclusion:** Based on the finding from this study, there were no significant deviations from pharmacopeia standards and specifications. The brands studied were safe enough and could be used to achieve the desired therapeutic effect.

**Keywords:** paracetamol, quality control, Gondar, Ethiopia

## Background

Paracetamol is a widely used over-the-counter analgesic and antipyretic drug. Chemically, it is a 4-hydroxyacetanilide (acetaminophen). Prostaglandins involvement has been proposed in the analgesic mechanism of paracetamol, by inhibition of central cyclooxygenases (COX-1, COX-2, and COX-3).<sup>1</sup>

Paracetamol or acetaminophen is active metabolites of phenacetin, also called coal tar analgesic which is no longer available on the market due to side effects. It is a white crystalline powder, odorless with a bitter taste and soluble in water.<sup>2</sup>

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Paracetamol is well absorbed from the proximal small intestine and is not subjected to significant first-pass metabolism. Its bioavailability is estimated between 63–89% in adults and approximately 90% metabolized by glucuronidation and sulphation to non-toxic metabolites in the liver and excreted through the urine.<sup>3</sup>

According to the definition of the International Organization for Standardization (ISO), “quality is a totality of features and characteristics of a product or service that bears its ability to satisfy stated or desired needs”.<sup>4</sup> The quality of the tablet is the collection of features and characteristics that contribute to its ability to meet given pharmacopeial requirements. Studies showed that self-medication with over-the-counter medications in the adult is record numbers.<sup>5,6</sup> Patients may lack the specialized knowledge to detect whether the product they are using is of good quality or not.<sup>7</sup> Counterfeited medications have can mislead especially if they are copied to make it look like the original product so that the patients are unlikely suspicious. According to WHO, (2017) the prevalence of fake medicines was higher in developing countries with weak regulations, enforcement, and scarcity of supply of essential medicines, unregulated market, and unaffordable prices.<sup>8</sup> For these reasons, the safety, quality, and efficacy of drug products especially in developing countries cannot be granted, therefore post-market qualitative studies are important.<sup>9</sup>

Paracetamol is being the most frequently counterfeited medication; studies have been conducted on its quality assessment in different countries.<sup>2,7,9–13</sup> Usually, a single generic drug is manufactured by different companies under different brand names. In many countries, the drug is also manufactured by small scale manufacturers which may be widely distributed or locally consumed. Paracetamol is one of a drug used for common ailments that are available as over the counter. It has been found in several studies that it is being consumed without proper prescription especially in rural areas.<sup>14,15</sup> Even though a single generic drug manufactured by different companies under different brand names should fulfill in the pharmaceutical parameters. The variations in the pharmaceutical parameter have a definite impact on the therapeutic effect of the drug that may not provide the expected result.<sup>12</sup>

Lacks of adequate quality control measures as well as the decomposition of the active component in the drug dosage form due to high temperature and humidity during storage have been identified as possible causes of treatment failure

and drug resistance. Besides, treatment failure has been frequently reported due to the inability of the regulatory body to ensure effective monitoring of the drug on the market.<sup>16</sup> Studies conducted in Addis Ababa and the Somali region of Ethiopia revealed the presence of paracetamol that did not fulfill the pharmacopeial requirements.<sup>12</sup> Thus this study was aimed to evaluate the quality of paracetamol tablet brands widely available in Gondar city.

## Methods and Materials

### Study Area and Period

The study was conducted from February to June 2018 at the University of Gondar, which is found in North of Gondar city, Ethiopia. Gondar city is located at 727 km from to the Northwest of Addis Ababa.

### Study Design

The experimental in-vitro study design was used to evaluate the in-vitro quality control parameter of the commercially available paracetamol tablet brands which are available in Gondar city. The study was conducted by performing various test procedures associated with the quality such as weight variations, hardness, and disintegration time, friability, dissolution profile, and content assay.

### Instruments

Instruments used were: analytical balance (model: JA203P; Bioway medical lab equipment co., Ltd, China), tablet hardness tester (PTB111E, Pharma Test), UV-spectrophotometer (LT-291, India), disintegration tester (Model B.J-3, Shangai Famo Machinery manufacture), dissolution test apparatus (RC-6, India), tablet grinder (Model 20–120, China), and PH meter (VSI-01ATC, VSI Electronics PVT. Ltd).

### Reagents Used

Potassium hydrogen Phosphate (KHPO<sub>4</sub>) (Shangi Chemex group Ltd), distilled water, reference standard paracetamol (Sigma-Aldrich, Featured Industry Pharmaceutical), and Hydrochloric acid (HCL) (Nutan chemicals, India).

### Sample Collection

Five variably popular paracetamol brands with a level claim of 500 mg were collected from UOG hospital pharmacy, government health centers, and private pharmacies in Gondar town, Ethiopia. About 102 paracetamol tablets were collected from each brand for the analysis. The product information such as manufacturer name, date of

manufacturing, expiry date at the time procurement and coded by number for each brand.

### Weight Variation Test

Twenty tablets were randomly selected from each brand and individually weighed using an analytical balance (Model: JA203P). The mean and standard deviation were calculated for the. Then the percentage of weight variation was calculated by using the following formula:

$$\% \text{ of weight variations} = \frac{\text{Average weight} - \text{individual weight}}{\text{Average weight}} \times 100$$

### Hardness

To conduct the hardness test, 10 tablets of each brand were randomly selected and the crushing strength of the tablets was measured. The average hardness of the tablet was calculated and the standard deviation was determined.

### Friability

For each of the brands, 10 tablets were selected and carefully dusted before testing, and weighed. Then the tablets were placed in the drum of friability tester and rotated at the speed of 25rpm for 4 minutes. After 100 revolutions and de-dusting, tablets were re-weighed and the friability percentage was calculated by the following equation;

$$\% \text{ Friability} = \frac{\text{weight before test} - \text{weight after test}}{\text{weight before test}} \times 100$$

### Disintegration Test

Six tablets were randomly selected from each brand and placed in the disintegration apparatus, which is filled by 900 mL of distilled water (disintegration medium) maintained at  $37 \pm 1^\circ\text{C}$ . The time taken to disintegrate the tablet and pass through the mesh was recorded and the mean of time taken was calculated.

### Dissolution Test

The dissolution test was conducted according to USP pharmacopeia. A buffer was prepared from potassium phosphate (pH 5.8) with a temperature maintained at  $37 \pm 1^\circ\text{C}$  throughout the experiment. The samples were withdrawn after 5, 10, 20, 30, 45, and 60 minutes and the equivalent amount of fresh buffer solution was immediately introduced as a replacement. The samples were filtered and assayed for drug content by measuring the

absorbance at 243nm using a UV spectrophotometer. Phosphate buffer was used as a blank.

### Assay of Paracetamol

Five tablets from each brand were randomly selected and weighed, then the tablets were powdered, and 125.84 mg, 115.56 mg, 114.52 mg, 134.16 mg, and 119.04 mg for code 1, 2, 3, 4, and 5 respectively were accurately weighed and transferred into 100 mL volumetric flask initially, 10 mL of phosphate buffer (PH 5.8) was added and shaken for 10 minutes. Thereafter, the volume was made up to 100 mL with buffer. Subsequently, the solution in a volumetric flask was filtered and 1 mL of the filtrate was diluted and analyzed at 243 nm using a UV- visible spectrophotometer. Then the absorbance of the resulting mixture at 243 nm was noted down and this was used to calculate the drug content.

The calibration curve was constructed from various concentrations of reference standards of paracetamol prepared in Phosphate buffer (PH 5.8). The concentration levels of 1, 2, 3, 4, 5,6,7,8,9,10 g/L were constructed against absorbance. The regression equation obtained was  $Y = 0.0802X + 0.0158$ , where  $Y$  is the absorbance, and  $X$  is the concentration. The correlation coefficient  $r^2 = 0.9971$  indicates a good correlation between absorbance and concentration of the reference sample (Figure 1).

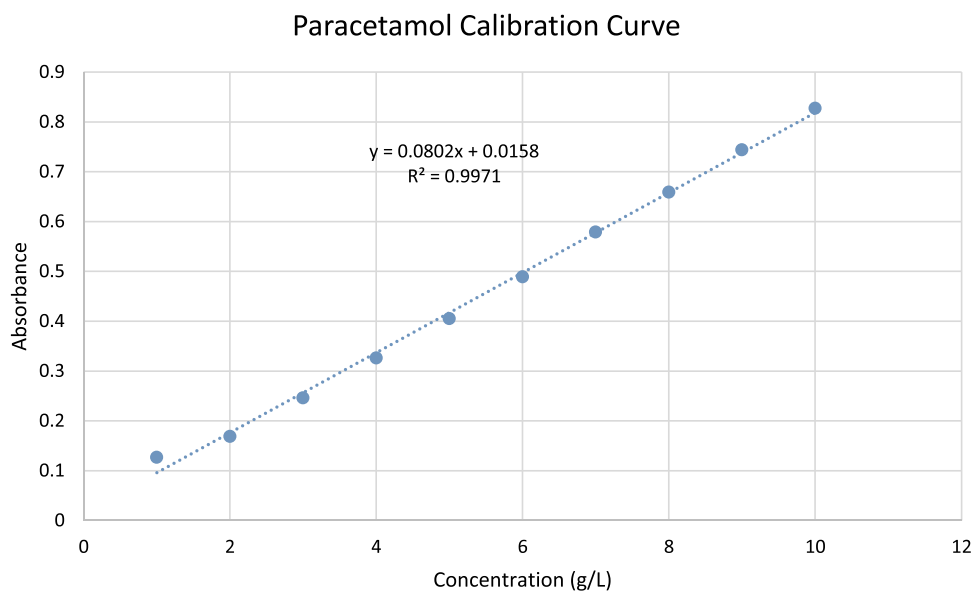
### Data Analysis

Data analysis was performed using Microsoft Excel 2010 and GraphPad prism version 5.01. The dissolution profiles and disintegration time of various brands of paracetamol were compared using one-way ANOVA and Dennett's multiple comparison tests were performed. P-value < 0.05 was considered statistically significant.

### Results

The study was conducted on popular bands of paracetamol marketed in Gondar city and the details of the brands are in Table 1. The results of physicochemical properties including weight variation, hardness, friability, disintegration, drug content, and dissolution of the five different brands of paracetamol tablets are presented in Table 2. Panadol was a highly friable brand followed by E-pharm (Table 2). Moreover, Paramol was the hardest and the thickest brands, and Para-denk had the highest brands with drug content (Table 2).

The drug release rate of paracetamol brands ranged from 70–99.5% (Figure 2). The one-way analysis of variance was



**Figure 1** Calibration curve of assay of paracetamol.

**Table 1** Name, Dosage, Manufacturer, Manufacturing Date and Expiration Date of Paracetamol Brands

Code	Name	Dosage	Manufacturer	Mfg. Date	Exp. Date
01	Paracetamol	500 mg	Ethiopian Pharmaceuticals Manufacturing (EPHARM)	02/2016	10/2020
02	Paramol	500 mg	Addis Pharmaceutical Factory – Adigrat	22/2017	11/2020
03	Cadimol	500 mg	Cadila Pharmaceuticals – Addis Ababa	10/2017	03/2020
04	Panadol	500 mg	GlaxoSmithKline Limited – Kenya	04/2017	04/2020
05	Para-denk	500 mg	Germany	01/2017	12/2021

**Table 2** Friability, Hardness, and Thickness, Weight Variation, and Assay of Different Paracetamol Brands in Gondar City

Code	Friability (%) n=10	Hardness ± SD n=10	Thickness (mm) ± SD n=10	Weight Variation (%) n=20	% of Drug Content, n=5
01	0.50 ± 0.003	174.40 ± 27.74	5.96 ± 0.06	1.08 ± 0.009	95.04 ± 3.41
02	0.63 ± 0.005	125.75 ± 15.80	5.90 ± 0.06	1.11 ± 0.008	102.69 ± 6.25
03	0.28 ± 0.006	173.90 ± 7.22	4.72 ± 0.03	0.89 ± 0.006	103.87 ± 5.64
04	0.07 ± 0.002	162.15 ± 8.86	5.85 ± 0.06	0.46 ± 0.004	103.87 ± 4.95
05	0.10 ± 0.001	117.00 ± 8.31	4.83 ± 0.02	0.75 ± 0.006	106.81 ± 4.63

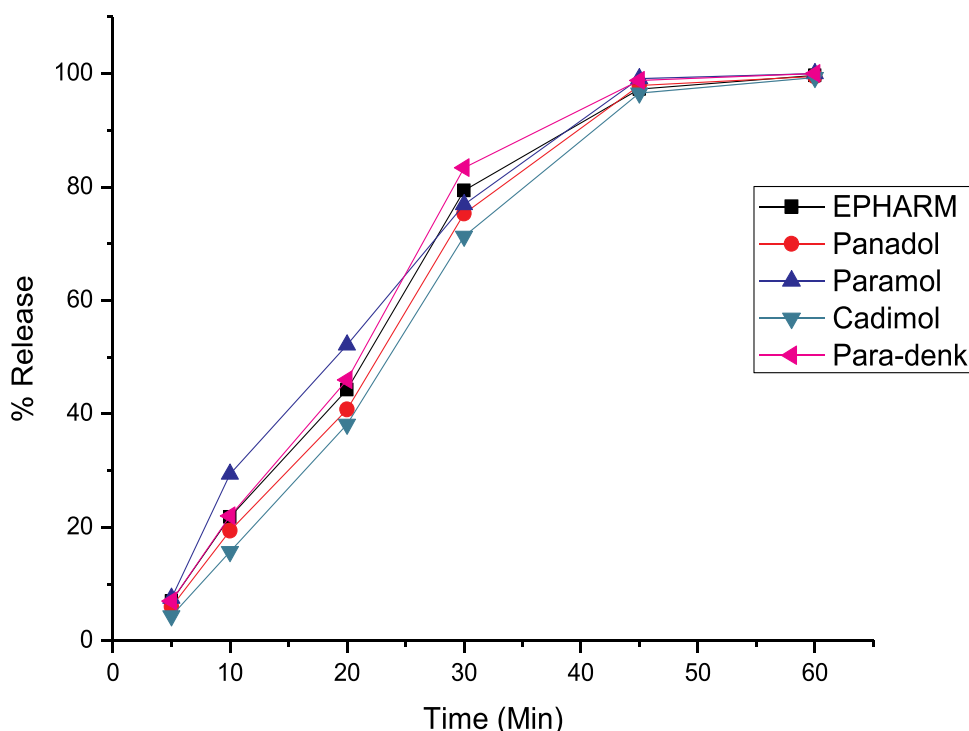
conducted for dissolution rate and disintegration rate in which code 1 set as a comparator. There were significant differences ( $p < 0.05$ ) in the drug release rate as compared to code 1 with all brands tested at 30 minutes. The disintegration time of different brands was also significantly different from the comparator (code 1) except code 2 (Figure 3).

## Discussion

The present study evaluated the different quality parameters of different brands of paracetamol. During this

research USP and BP pharmacopeia procedures were used to conduct each test.<sup>17,18</sup> A total of five paracetamol brands marketed in Gondar city were evaluated for weight variation, hardness, disintegration time, friability, dissolution, and content uniformity.

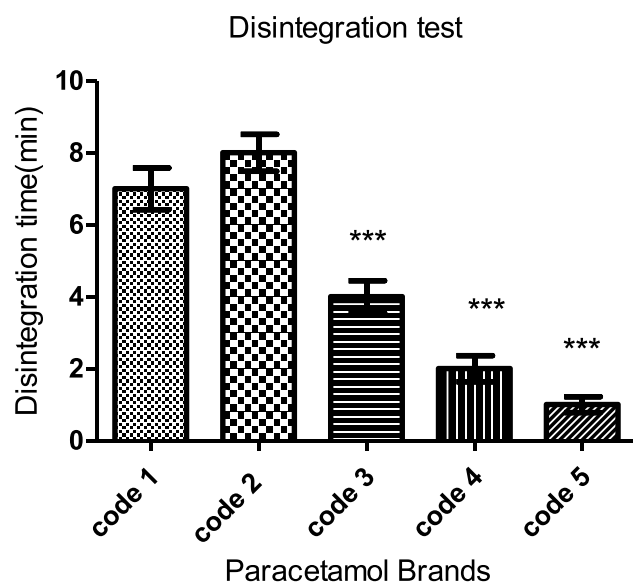
In this study, the weight variation which is the key to controlling the crushing strength and friability of tablet was assessed. The weight variation which is the key to controlling the crushing strength and friability of the tablet was assessed. The percent average weight variation of all the five brands



**Figure 2** Dissolution profile of five brands of paracetamol tablet in phosphate buffer (5.8).

ranged from 0.4596 to 1.113% all the results obtained for weight variation falls within the acceptable weight variation range of 5%.<sup>17</sup> Thus, the test stated that the samples of both locally manufactured (Paramol, cadimol, and Paracetamol) and multinational paracetamol brands (Panadol and Para-denk) have passed the weight variation uniformity test as

specified in the USP, no brand deviate by 5% of the average weight. A variation beyond the pharmacopeia limits indicates unacceptable pharmaceutical products and corresponding variation in the drug content. Similar to our findings, in a study conducted in Pakistan to analyze, compare, and evaluate the quality standards of commercially available brands of acetaminophen tablets, all the three brands (Panadol, Calpol, and Febrol) available in Karachi met the USP specification for weight variation, implying the content uniformity although weight uniformity is not confirmatory test.<sup>11</sup>



**Figure 3** Disintegration time of paracetamol brands. Code 1 was a comparator; \*\*\* indicates p- value < 0.0001.

Tablets could be able to resist abrasion when subjected to stresses from collision and tablet sliding towards one another and other solid substances, which can result in the removal of small fragments from tablets' surface. It is usually measured by a friability tester. In the friability test, the friability values for paracetamol tablet brands ranged from 0.074 to 0.63%. All five brands of paracetamol have passed the friability test and have met the specification of USP which specifies that any brand they must not lose more than 1% of their initial weight.<sup>18</sup> The result may further indicate the resistance of the tablets to the external pressure from manufacturing, shipping, and transportation. At the same time, high strength should not compromise the dissolution of the drug in the stomach. But high tablet strength should not compromise disintegration in the stomach which is essential to achieve immediate drug release.

The study showed that the average compression force recorded was in the range of 117–174.7 Newton, which is above the minimum value of 50 N. Since the hardness and disintegration of a tablet related, it is essential that the hardness of a tablet has to be within the acceptable range. Tablets with increased hardness values tend to have increasing disintegration time, whereas tablets with decreased hardness are more friable and take less time to disintegrate.

The disintegration time was performed to evaluate the time required for a drug to disintegrate in the gastric environment. It also shows the drug release profile of the drugs. Paracetamol tablet was expected to disintegrate within 15 minutes.<sup>18</sup> According to this study the mean disintegration time ranged from 01 minutes to 08 minutes which is less than the standard disintegration time which is 15 minutes for uncoated tablets.<sup>18</sup> One way analysis of variance showed that there was a significant difference in disintegration time between Paracetamol (E-pharm) and Paramol, cadimol, and Para-denk  $P < 0.05$ . Various studies conducted in Malaysia, Palestine, Pakistan, Bangladesh, and India have investigated brands of paracetamol and fulfilled the requirements on USP for disintegration time.<sup>3,7,19–21</sup>

Dissolution was another parameter directly related to the absorption and bioavailability of the drug. Drugs with poor dissolution profiles will not be sufficiently available in the body to produce the desired therapeutic outcome. The release rate of different paracetamol brands ranged from 70% - 99.5%. Para-denk (05) and Paramol (02) showed the highest percentage of drug release of the entire sample which was 99% and Panadol showed 98% followed by Cadimol which was 90% drug release. The result of one-way analysis variance (ANOVA) at 95% CI at 30 minutes indicated that there was a significant difference in drug release between brands of paracetamol tested ( $P$ -value  $< 0.05$ ). This shows different brands of paracetamol were not equivalent in respect to in-vitro drug release. Dunnett's test was performed between the comparator paracetamol (E-pharm) and other brands at 95% CI. All brands had a significant difference from the comparator ( $P$ -value  $< 0.05$ ). Similar to this study, research conducted on different brands of paracetamol tablets in Sarhad University of Science and Information Technology, Pakistan, showed that the results of the dissolution test were found to be similar and satisfy BP specifications.<sup>22</sup> In another study undertaken in Trinidad and Tobago on four brands of paracetamol, the results of all parameters of different brands were in pharmacopeial limits.

The result of an assay for the active ingredient (Table 2) obtained from five brands of paracetamol indicated that the

maximum content was seen with Para-denk (106.81) and the minimum was E-pharm (95.04). All products contained paracetamol in a range of 100%  $\pm$  10% of a label claim. According to USP pharmacopeia, paracetamol content should not be less than 90% and greater than 110%.<sup>18</sup> Therefore, all brands studied complied with USP pharmacopeial requirements.

Therefore, it could be concluded that marketed pharmaceutical tablets of paracetamol of these brands are safe, and satisfy the quality control limit of pharmacopeia.<sup>23</sup> Therefore, it is evident from the study that most of the brands tested showed good results. The proper authority needs to take further necessary steps to ensure the continuity in the establishment of the product quality.

In the Somalia region of Ethiopia, the results of the study on the quality of legal and illegal brands of paracetamol showed that the quality of illegally marketed tablets was below the standard in contrast to the legal paracetamol tablets which is hazardous to the community. Each illegal drug was failed to comply with at least one quality parameter out of five.<sup>12</sup>

According to WHO, an estimated 700 deaths annually are caused by fake pharmaceutical agents suggesting that the total annual mortality due to this treatment will be much higher.<sup>24,25</sup> About 2500 people died in the Niger state of Nigeria following the administration of counterfeits of meningococcal-vaccines (containing no active ingredient). Acute renal failure due to poisoning from diethylene glycol packaged as a cough syrup which resulted in hundreds of deaths in Nigeria.<sup>9</sup> All of these findings suggest the necessity for undertaking quality control parameters for every pharmaceutical product, not just paracetamol.

## Conclusion

Various quality control parameters for tablets like weight variation, friability, disintegration time, assay, and dissolution tests were conducted in this study. This study revealed that all brands of paracetamol studied met the USP specification. Multinational products showed the lowest friability values. Generally, all brands complied with the standard specification. The post-market evaluation is essential to monitor the approved medicine to adequately assess the quality, therapeutic effectiveness, and safety of medicines for the end-user.

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## Author Contributions

All authors have made a significant contribution to the work reported including the conception, study design, execution, and acquisition of data, analysis, and interpretation. All authors took part in drafting, revising, and critically reviewed the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest for this work.

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